

REMARKS**I. Status of Claims**

Claims 17-22 and 24-30 are pending in the present application. Claims 26-27, and 30 are allowed. Claims 24 and 28 have been amended. Claims 17-19, 21-22, and 24-25, are rejected, and claim 20 is objected to. Claim 29 is withdrawn.

Claim 24 has been amended to recite “wherein said carrier is polylactic acid or polyglycolic acid.” Support for this amendment may be found at least at page 4, lines 5-12 of the specification, and originally filed claim 9.

Claim 28 has been amended to recite “wherein said composition further comprises a carrier, wherein said carrier is polylactic acid or polyglycolic acid.” Support for this amendment may be found at least at page 3, lines 8-15 of the specification and originally filed claim 6.

No new subject matter has been added, thus entry of the amendments is respectfully requested.

II. Objection to Specification

The specification is objected to for allegedly failing to provide proper antecedent basis for the claimed subject matter. Specifically the Office alleges that the limitation “a second carrier comprising polylactic acids or polyglycolic acids and the adjuvant” in claim 24, and the limitation “a second carrier comprising polylactic acids or polyglycolic acids” in claim 28 lack clear support or antecedent basis in the specification.

Applicants respectfully traverse the objection and its supporting remarks. However, in order to advance prosecution, but without prejudice or disclaimer, Applicants have amended claim 24 and claim 28.

Claim 24 has been amended to recite “wherein said carrier is polylactic acid or polyglycolic acid.” As amended, claim 24 finds clear support at page 4, lines 5-12 of the application, which states that NmC may be conjugated to a carrier that is polylactic acid or polyglycolic acid.

Claim 28 has been amended to recite “wherein said composition further comprises a carrier, wherein said carrier is polylactic acid or polyglycolic acid.” As amended, claim 28 finds clear support in originally filed claim 6, which states that an immunogenic composition comprising NmC and a first carrier (*i.e.*, CRM197) and NmB can also comprise a second carrier. Furthermore the specification at page 3, lines 8-15, indicates that a carrier can be polylactic acids or polyglycolic acids.

Applicants respectfully request that this objection to the specification be withdrawn.

III. Rejections under 35 U.S.C. § 103(a) Maintained

Claims 17-19, 22 and 25

Claims 17-19, 22 and 25 are rejected under § 103(a) as allegedly being unpatentable over Granoff *et al.* (*infect. Immun.* 65: 1710-1715, May 1997, of record) (Granoff *et al.*, 1997) in view of Granoff *et al.* (*J. Pediatr.* 121: 187-194, 1992) (Granoff *et al.*, 1992), Vella *et al.* (*Biotechnology* 20: 1-22, 1992) and Frasch (*In: Development and Clinical Uses of Haemophilus B conjugate Vaccines*. (Ed) Willis *et al.* M. Dekker, New York, pages 435-453, 1994).

To the extent the rejection applies to the amended claims, Applicants respectfully traverse the rejection and its supporting remarks.

The Office has not established a *prima facie* case of obviousness. As noted in the previous Response (dated September 11, 2009), the Office has acknowledge that Granoff *et al.*, 1997 does not teach the presence of outer membrane vesicles from serogroup B *Neisseria meningitidis* in their immunogenic vaccine composition. Therefore, Applicants maintain that Granoff *et al.*, 1997 provides no information as to the interaction between MF59 and NmB OMVs. Similarly, Granoff *et*

al., 1992 does not teach the presence of MF59 in their immunogenic vaccine compositions. Therefore, Granoff *et al.*, 1992 also fails to provide any information regarding the interaction between MF59 and NmB OMVs. MPEP § 2143 states that “combining known prior art elements is not sufficient to render the claimed invention obvious if the results would not have been predictable to one of ordinary skill in the art.” Applicants thus maintain that one of skill in the art could not predictably combine Granoff *et al.*, 1997 with Granoff *et al.*, 1992 to produce the instant invention as neither provides any indication of how MF59 and NmB OMVs interact with one another.

In response to Applicants’ arguments, the Office has asserted that the pending claims do not require the recited MF59 to interact with the OMVs in a specific manner, and that the teachings of Granoff *et al.*, 1997 as modified by Granoff *et al.*, 1992, Vella *et al.*, and Frasch taught the claimed composition. However, Applicants respectfully point out that regardless of whether the pending claims require a specific interaction with MF59, the fact remains that one of skill in the art would not have been able to predict that combining the Hib-NmB OMV conjugate taught by Granoff *et al.*, 1992 with the MF59 adjuvant taught by Granoff *et al.*, 1997 would result in the expected benefits of using MF59 (see Granoff *et al.*, 1997, right column of page 1714). Indeed Granoff *et al.*, 1997 acknowledge that there was uncertainty regarding using MF59 with polysaccharide-protein conjugate vaccines (last paragraph on left column of page 1714). Given that Granoff *et al.*, 1992 teach a Hib *polysaccharide* conjugated with NmB OMVs, one of skill in the art would not have predicted that the suggested combination of Hib-NmB, NmC-CRM₁₉₇, and MF59 would work as described in the application at the time the claimed invention was made (see *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1741, 82 USPQ2d 1385, 1396 (2007)).

The Office also alleges that nowhere do the applied prior art references indicate that MF59 would eliminate the immunogenicity of the NmB OMVs, and that, as acknowledged by Applicants, even with the MF59 present, the immunogenicity of the NmB OMVs was maintained at a sufficient level. Applicants respectfully assert that the Office is using impermissible hindsight to support the rationale of combining the teachings of Granoff *et al.*, 1997 and Granoff *et al.*, 1992. MPEP § 2141.01 III makes clear that the content of the prior art is determined at the time the invention was made to avoid hindsight.

The Office has not demonstrated that *prior* to Applicants' disclosure, one of skill in the art would have combined the teachings of Granoff *et al.*, 1997 and Granoff *et al.*, 1992 to construct the claimed invention. As noted above, neither Granoff reference teaches the use of MF59 with NmB OMVs. Furthermore, Applicants' acknowledgement of NmB OMV immunogenicity being maintained at a sufficient level in the presence of MF59, was an acknowledgement of a fact established in the present application, *not* the cited references or the prior art. Thus, given the unpredictability of using MF59 (right column on page 1714 of Granoff *et al.*, 1997), one of skill in the art would have had no reason to combine PRP-OMP with NmC oligosaccharide and MF59. Moreover, without a reason to combine the references, as well as a lack of a predictable result, the only conclusion supported by the record is that the rejection was made impermissibly using hindsight reconstruction of the invention.

For at least the reasons set forth above, Applicants respectfully assert that claims 17-19, 22 and 25 would not be obvious in view of Granoff *et al.*, 1997, Granoff *et al.*, 1992, Vella *et al.*, and Frasch. Therefore, Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) be withdrawn.

Claims 18 and 19

Applicants maintain that the rationale provided by the Office applies even to a lesser extent for claims 18 and 19, which require that the capsular oligosaccharide from serogroup C *N. meningitidis* (NmC) be conjugated to a protein carrier. In response to Applicants' arguments, the Office asserts that Applicants' argument on this issue is not relevant to the rejection of record, because the rejection did not set forth conjugating NmC to OMV for the expected benefit of increasing immunogenicity, and the Office Action did not state that claims 18 and 19 read upon a modified vaccine composition where both the NmC and Hib are conjugated to OMVs.

Applicants respectfully assert that even if the Office did not set forth conjugating NmC to OMVs, the expected benefit of increased immunogenicity taught Granoff *et al.*, 1992 would have led one of skill in the art to modify the NmC conjugate of Granoff *et al.*, 1997. Furthermore, absent

impermissible hindsight reconstruction of the claimed invention, the teachings of Granoff *et al.*, 1992 would not have led one of skill in the art to combine the PRP-OMP conjugate with NnC-CRM₁₉₇ and MF59. As noted by the Office on page 6 of the Office Action dated April 20, 2009, the Hib-NmB OMV conjugate elicited earlier acquisition of serum antibody than did the Hib-CRM₁₉₇ conjugate. However, Granoff *et al.*, 1992 gives no indication as to whether the NmB OMV would elicit that same early acquisition of antibodies in combination with polysaccharide conjugate (*i.e.*, NnC-CRM₁₉₇) and an MF59 adjuvant. Given this lack of guidance, one of skill in the art would have been more likely to reduce the number of variables by conjugating NmB OMVs to both Hib and NnC, than to combine PRP-OMP with the NnC-CRM₁₉₇ and MF59, as suggested by the Office. Thus, it would appear that the Office is using the teachings of the present application to support the conclusion that one of skill in the art would have had reason to pick and choose specific elements of the Granoff references to reconstruct the claimed invention. However, as stated by the Court of Appeals for the Federal Circuit “[o]ne cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention,” *In re Fine*, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988).

In response to the Office’s allegation that Granoff *et al.*, 1997 suggested the use of MF59 in combination with other vaccines (first full paragraph in right column of page 1714), Applicants respectfully point out that the paragraph cited by the Office refers back to the introduction section on page 1710, which states that MF59 has been used with recombinant glycoprotein subunit vaccines for herpes simplex virus type 2, cytomegalovirus, HIV, and inactivated influenza vaccine. Applicants note that none of the listed vaccines include NmB OMV.

The Office further alleges that Applicants’ argument on the alleged lack of reasonable expectation of success was not persuasive, because Granoff’s (1997) conjugate composition containing MF59 induced higher capsular antibodies even after the first dose and Granoff’s (1992) Hib-OMV conjugate also induced acceptably high levels of antibodies after three doses.

Applicants respectfully maintain their traversal on the ground that there would be no reasonable expectation of success in combining NnC-CRM₁₉₇ with Hib-OMV and MF59 to obtain

the benefits of a strong immune response to both capsular polysaccharides after a single injection. However, as discussed above, Applicants also respectfully assert that one of skill in the art would not have predicted that results of such a combination (MPEP § 2143). Granoff *et al.*, 1992 teach that the Hib-OMV conjugate induced increased levels of antibodies after a single dose. However, three doses of the Hib-CRM₁₉₇ conjugates were required to induce similar levels of antibodies (see Fig. 1). Thus it would be unpredictable whether combining the Hib-OMV conjugate of Granoff *et al.*, 1992 with NmC-CRM₁₉₇ and MF59 would result in increased levels antibodies after a single injection.

The Office has also failed to demonstrated how Vella *et al.* or Frasch impacts the predictability of combining the teachings of Granoff *et al.* 1997 and Granoff *et al.* 1992 to yield the claimed invention.

For at least the reasons set forth above, Applicants assert that claims 18 and 19 would not be obvious in view of Granoff *et al.*, 1997, Granoff *et al.*, 1992, Vella *et al.*, and Frasch. Therefore, Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) be withdrawn.

Claim 21

The rejection of claim 21 under § 103(a) as allegedly being unpatentable over Granoff *et al.*, 1997 as modified by Granoff *et al.*, 1992, Vella *et al.*, Frasch, and further in view of Dalseg *et al.* (In: Vaccines 96. (Ed) Brown F. Cold Spring harbor Laboratory Press, Cold Spring Harbor, N.Y., pages 177-182, 1996, of record) is maintained.

Applicants respectfully traverse the rejection and its supporting remarks. As discussed above, the Office has failed to establish a *prima facie* case of obviousness, because the Office has not shown that combining the teachings of the references would yield a predictable result. The Office has not demonstrated how Dalseg *et al.* impacts the predictability of combining the teachings of Granoff *et al.* 1997 and Granoff *et al.* 1992 to yield the claimed invention. Applicants therefore respectfully request that this rejection under 35 U.S.C. § 103(a) be withdrawn.

Claim 24

Claim 24 is rejected under § 103(a) as allegedly being unpatentable over Granoff *et al.*, 1997 as modified by Granoff *et al.*, 1992, Vella *et al.*, Frasch, and further in view of Seid (US 6,638,513, of record) ('513) or Granoff (WO 98/58670) ('670).

Applicants respectfully traverse the rejection and its supporting remarks. As discussed above, the Office has failed to establish a *prima facie* case of obviousness, because the Office has not shown that combining the teachings of the references would yield a predictable result. The Office has not demonstrated how Seid ('513) or Granoff ('670) impacts the predictability of combining the teachings of Granoff *et al.* 1997 and Granoff *et al.* 1992 to yield the claimed invention. Applicants therefore respectfully request that this rejection under 35 U.S.C. § 103(a) be withdrawn.

IV. Rejection under 35 U.S.C. § 112, First Paragraph (New Matter)

Claims 24 and 28 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, has possession of the claimed invention.

Applicants respectfully traverse the rejection and its supporting remarks. However, in order to advance prosecution, but without prejudice or disclaimer, Applicants have amended claim 24 and claim 28. As discussed above in the "Objection to the Specification" section, clear descriptive support for amended claim 24 may be found at least at page 4, lines 5-12 of the specification; and support for amended claim 28 may be found at least in claim 6 as originally filed and at page 3, lines 8-15 of the specification.

Applicants thus respectfully request that the rejection under 35 U.S.C. § 112, first paragraph, be withdrawn.

V. Rejection under 35 U.S.C. § 112, Second Paragraph

Claim 28 is rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite, because the recitation of “a second carrier” in claim 28 is indefinite because claim 26, from which claim 28 depends, does not recite a first carrier.

Applicants respectfully traverse the rejection and its supporting remarks. However, in order to advance prosecution, but without prejudice or disclaimer, Applicants have amended claim 28 to remove reference to “a second carrier.” As amended, claim 28 is directed to the composition of claim 26, wherein said composition comprises a carrier.

Applicants thus respectfully request that the rejection under 35 U.S.C. § 112, second paragraph, be withdrawn.

VI. Objection to the Claims and Allowable Claims

The Office has objected to claim 20 as being dependent upon a rejected base claim, but found that the claim would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. For the reasons stated above, Applicants respectfully assert that the objected claim depends from an allowable claim. Applicants therefore respectfully request that this basis for objection be withdrawn.

CONCLUSION

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 03-1952 referencing docket no. 223002100100. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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